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Transoral laser microsurgery versus radiation therapy in the management of T1 and T2 laryngeal glottic carcinoma: which modality is cost-effective within the UK?

Matthew Prettyjohns, Stuart Winter, Cyrus Kerawala, Vinidh Paleri

On behalf of the NICE cancer of the upper aerodigestive tract guideline committee:

Martin Robinson, Cyrus Kerawala, Shreerang Bhide, Margred Capel, Leah Cox, Michael Fenlon, Laurence Newman, Sarah Orr, Tom Roques, Anthony Smith, Stephen Spraggett, Bella Talwar, Selvam Thavaraj, Jane Thornton, Wai Lup Wong

Matthew Prettyjohns, Senior Health Economist, National Collaborating Centre for Cancer, Cardiff, CF10 3AF

Cyrus Kerawala, Consultant Head and Neck Surgeon, Royal Marsden Hospitals, London, SW3 6JJ

Stuart Winter, Consultant Head and Neck Surgeon, Oxford University Hospitals, Oxford, OX3 9DU

Vinidh Paleri, Honorary Professor and Consultant in Head and Neck Surgery, Newcastle upon Tyne Hospitals, Newcastle upon Tyne, NE7 7DN

Corresponding author:
Vinidh Paleri, MS, FRCS (ORL-HNS), Professor of Head and Neck Surgery, Department of Otolaryngology–Head and Neck Surgery, Newcastle upon Tyne Foundation Hospitals NHS Trust, Newcastle upon Tyne, U.K.
vinidh.paleri@newcastle.ac.uk

Objectives - T**o** identify the most cost effective treatment strategy in patients with early stage (T1and T2) cancers of the laryngeal glottis.

Design - A Markov decision model populated using data from updated systematic reviews and meta analyses, with attributable costs from NHS sources. Data on local control and mortality was obtained from updates of existing systematic reviews conducted for the NICE guideline on cancer of the upper aerodigestive tract. Procedure costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate health resource group code

Setting – The UK National Health Service

Population - Patients with early stage (T1 and T2) cancers of the laryngeal glottis

Interventions - Transoral laser microsurgery (TLM) and radiation therapy (RT)

Main outcome measures – Total costs, incremental costs and quality adjusted life years (QALYs) over a ten-year time horizon.

Results - RT as the initial treatment strategy was found to be more expensive (£2,654 vs £623) and less effective (QALY reduction of 0.141 and 0.04 in T1a and T1b-T2 laryngeal cancer respectively) than TLM. The dominance of TLM for T1a cancers was unchanged in most scenarios modelled in sensitivity analysis. For T1b-T2 laryngeal cancers, the result changed in numerous scenarios. In probabilistic sensitivity analysis, TLM was found to have a 71% and 58% probability of being cost-effective in T1a and T1b-T2 laryngeal cancer, respectively.

Conclusions - TLM is a cost effective strategy to adopt in the management of T1a laryngeal cancers. Uncertainty remains over the optimal strategy to adopt in T1b-T2 laryngeal cancers.

Introduction

Early carcinomas of the laryngeal glottis (T1 and T2 tumours) are typically treated with either radical radiotherapy (RT) or transoral laser microsurgery (TLM). Although level 1 evidence is lacking, the literature is replete with studies that confirm both modalities are equally effective from an oncologic perspective[1]. It is inevitable that the side-effect profile of these treatment modalities will be different in the short term, but no studies have categorically revealed differences in functional outcomes using existing measures. The data and experience accumulated regarding the treatment of this disease has resulted in most patients with mid-cord lesions being offered TLM; however, when the tumour reaches the anterior commissure, surgical resection of this area can have greater effects on the voice, and RT may be the preferred option.

There is little evidence to demonstrate cost-effectiveness of either treatment modality within the UK heath care system. The aim of this analysis was to estimate the cost-effectiveness of initial treatments for newly diagnosed T1 or T2 carcinoma of the laryngeal glottis in the National Health Service (NHS) in the UK. The analysis was conducted as part of the National Institute for Health and Care Excellence (NICE) guideline on cancer of the upper aerodigestive tract (NG36)[1].

Methodology

A de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel (figures 1 and 2).

Patients newly diagnosed with T1-T2 carcinoma of the larynx enter the model and receive primary tumour treatment with either RT or TLM. Following treatment with RT, there is a small chance that patients may have a non-functioning larynx that necessitates a subsequent total laryngectomy, after which the patient will be monitored in a follow-up programme. All other patients treated with either TLM or RT will be entered into a follow-up programme. There is then a chance that the patient may develop recurrence at which point further treatment with one of multiple treatment options would be given. The proportion of patients receiving each of the treatment options was estimated by the guideline committee and are discussed in greater detail in a later section of the report. It should be noted that the subsequent treatment options are dependent upon preceding treatments (for example RT is an option for recurrent tumours in patients initially treated with TLM but not for patients initially treated with RT).

Following treatment of a recurrent tumour, the patient is once again monitored in a follow-up schedule where further recurrences may be detected and treated with one of multiple treatment

options. This pattern continues until the patient undergoes a total laryngectomy at which point treatments for localised disease have been exhausted. Patients could die from cancer of the upper aerodigestive tract or other cause mortality at any point in the process.

Recurrence rates for T1a laryngeal cancer patients undergoing RT or TLM were estimated using data on progression free survival from the clinical evidence review conducted for the NICE guideline on upper aerodigestive tract cancers. A meta-analysis[1] of 14 observational studies[2-15] in 1855 patients with stage T1a disease was the primary source of data. The recurrence rate for patients treated with RT was based upon the local control rate of 89.3% observed in patients receiving this treatment. A relative risk of 0.99 was then estimated and this used to estimate local control rates in patients treated with TLM (88.5%). These values were then converted to annual recurrence rates of 2.05% and 2.21% for patients treated with RT and TLM, respectively (assuming a constant rate of recurrence over the follow-up period).

While differences in recurrence rates have been modelled in the base case, it should be noted that the slight difference in local control rates was not found to be statistically significant. The uncertainty around the difference in local control rates was explored in sensitivity analysis.

In the absence of high quality comparative evidence for the T1b-T2 laryngeal group, observational evidence was used. A systematic review by O'Hara et al[16] found that 3-year local control rates were lower in patients treated with TLM (76.8%) rather than RT (86.2%). These were converted to annual recurrence estimates of 6.56% and 2.99% for the TLM and RT arms respectively (assuming a constant rate of recurrence over the time period).

It was assumed that there were no recurrences after five years of being recurrence free. This is intended to reflect clinical practice where recurrences after this time period are very rare.

Disease-related mortality was captured in the model using data from a meta-analysis[1] of 11 observational studies[3-6,8-10,12-15] in patients with stage T1a disease treated with TLM and RT. An odds ratio (OR) of 1.55 was reported for disease specific survival, suggesting a slight benefit in patients treated with TLM. However, as above, this difference in survival was not found to be statistically significant (OR 95% CI 0.75 to 3.20). It was therefore assumed that there was no difference in disease specific mortality in the base case analysis.

A combined mortality rate was estimated using the disease specific survival observed in T1a patients treated with RT or TLM in the studies (98.0% over a follow-up period of 5-139 months). This value was then converted to an annual mortality rate of 0.4% (assuming a constant rate of mortality over the follow-up period). In the base case, these values were also applied to T1b-T2 laryngeal cancer patients. However, alternative mortality rates were explored in one-way sensitivity analysis. Death from other

causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS)[17].

There are numerous treatment options available for patients that experience recurrence. The treatment proportions for recurrent patients that were initially T1a and treated with RT were estimated from a survey of current UK practice by Paleri et al. 2012 (personal communication). All other treatment proportions for recurrent patients were estimated by the guideline committee based on their experience in clinical practice. The treatment proportions following recurrence are shown in tables 1 and 2 for patients initially treated with RT and TLM, respectively.

Table 1: Post-recurrence treatment options for patients with T1a and T1b-T2 cancer of the laryngeal glottis initially treated with radiotherapy

Treatment	After first recurrence	After second recurrence	After third recurrence
T1a laryngeal cancer			
Total laryngectomy	78%	78%	92%
Partial laryngectomy	7%	7%	8%
TLM	15%	15%	0%
Radiotherapy	0%	0%	0%
T1b-T2 laryngeal cancer			
Total laryngectomy	90%	90%	92%
Partial laryngectomy	7%	7%	8%
TLM	3%	3%	0%
Radiotherapy	0%	0%	0%

Table 2: Post-recurrence treatment options for patients with T1a and T1b-T2 cancer of the laryngeal glottis initially treated with TLM

Treatment	After TLM		After radiotherapy	After partial laryngectomy *
	First recurrence	Second recurrence		
T1a laryngeal cancer				
Total laryngectomy	20%	27%	85%	75%
Partial laryngectomy	15%	20%	15%	0%
TLM	25%	0%	0%	0%
Radiotherapy	40%	53%	0%	25%
T1b-T2 laryngeal cancer				
Total laryngectomy	30%	32%	85%	75%
Partial laryngectomy	15%	16%	15%	0%
TLM	5%	0%	0%	0%
Radiotherapy	50%	53%	0%	25%

Treatment	After TLM		After radiotherapy	After partial laryngectomy *
	First recurrence	Second recurrence		
T1a laryngeal cancer				

*In patients without previous radiotherapy

The model estimates total costs and total quality adjusted life years (QALYs) for each treatment strategy over the modelled time horizon of ten years, with future values discounted at a rate of 3.5% per year as recommended by NICE. The total costs include the cost associated with any treatment, monitoring or management strategy that patients undergo. QALYs are the measure of effectiveness used in the analysis and they were estimated by combining life year estimates with utility values (or QoL weights) associated with being in a particular health state. A full list of the cost and QoL inputs applied in the model are detailed in Table 3.

Table 3: Cost and QoL inputs in the model

Parameter	Value	Reference
TLM treatment cost	£2,034.92	[18]
Radiotherapy cost	£3,429.56	[18]
Intensity modulated radiotherapy (IMRT) cost	£5,410.96	[18]
IMRT with concomitant radiotherapy cost	£6,069.11	[18] & [20]
Partial laryngectomy cost	£10,578.56	[18]
Total laryngectomy cost	£14,181.18	[18]
Valve change costs per annum (after laryngectomy)	£600.00	Guideline committee estimate
Systemic chemotherapy cost	£3,555.10	[18] & [20]
Palliative care cost	£7,287.00	[21]
Follow-up costs		
Average number of follow-up sessions in year 1 after TLM	8.58	Guideline committee estimate
Average number of follow-up sessions in year 1 after RT	7.58	Guideline committee estimate
Average number of follow-up sessions in year 2	5.85	Guideline committee estimate
Average number of follow-up sessions in year 3	3.90	Guideline committee estimate
Average number of follow-up sessions in year 4	2.00	Guideline committee estimate
Cost per consultation	£86.92	[18]
Nasendoscopy	£115.09	[18]
Speech and language therapy and dietetics costs		
Average number of sessions during and after TLM	5	Guideline committee estimate

Parameter	Value	Reference
Average number of sessions during and after RT	10	Guideline committee estimate
Average number of sessions during and after partial laryngectomy	16	Guideline committee estimate
Average number of sessions during and after total laryngectomy	16	Guideline committee estimate
Cost per speech and language therapy consultation	£120.22	[18]
Cost per dietetics consultation	£80.81	[18]
QoL Values		
Alive with voice box entirely intact	0.8718	[22]
Alive with part of voice box intact	0.7060	[22]
Alive without voice box	0.8050	[22]
End of life (metastatic disease)	0.7363	[23]

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and personal social services were included. These costs include drug costs, treatment costs and any other resource use that may be required. Where possible, all costs were estimated in 2013-14 prices. The majority of costs were sourced from NHS reference costs 2013/14[18] by applying tariffs associated with the appropriate health resource group (HRG) code. Drug costs were calculated using dose and regimen information from the British National Formulary (BNF)[19] and guideline committee with unit costs sourced from the electronic market information tool (eMit)[20].

The total cost of initial RT was estimated to be £3,430, based upon preparation and delivery costs from NHS reference costs[18] and assuming that 20 fractions of complex conformal radiotherapy would be delivered in the outpatient setting. The cost of TLM was estimated to be £2,035, based upon the average inpatient cost of an 'intermediate mouth or throat procedure'[18].

For those patients receiving a TLM or conventional RT as salvage treatment, the same costs estimated for initial treatment were applied. However, patients with late stage recurrences (T3 or T4) undergoing RT (estimated to be 30% in the base case) were assumed to receive intensity modulated radiotherapy (IMRT). The cost of IMRT was estimated to be £5,411, based upon preparation and delivery costs from NHS reference costs[18], assuming that 30 fractions would be delivered in an outpatient setting. It was further assumed that 50% of patients undergoing IMRT would receive concomitant chemotherapy with cisplatin given in two doses of 100mg/m^2 at an estimated cost of £658[20].

The costs of salvage treatment with a partial laryngectomy (£10,579) or total laryngectomy (£14,181) for patients that experience a recurrence were sourced from NHS Reference costs[18]. It was assumed

that adjuvant IMRT would be performed for 60% of patients undergoing total laryngectomy if they have not previously been irradiated. It was further assumed that 50% of those patients that receive IMRT would receive concomitant chemotherapy with two doses of cisplatin.

The cost per follow-up consultation was estimated to be £86.92 based upon the average cost of an ENT and Maxillofacial surgery attendance from NHS reference costs[18]. It was also assumed that a nasendoscopy would be performed at each visit which, based on NHS reference costs, was estimated to cost £115.09[18]. The number of follow-up visits typically required after each treatment was estimated by the guideline committee.

Based on the average cost of attendances from NHS reference costs, a dietetics session and speech and language therapy session were estimated to cost £80.81 and £120.22, respectively[18]. The number of sessions required after each treatment modality were estimated by the guideline committee.

Local audits report that the costs associated with the regular valve changes required in patients after a total laryngectomy range from £530-£670 per patient per annum (personal communication with guideline committee member). For the purpose of the base case analysis the midpoint of £600 was used with variations explored in sensitivity analysis.

A metastatic cancer state was not explicitly modelled as such. However, it was assumed that patients that die from upper aerodigestive tract cancer were likely to have developed metastatic disease. Thus, the costs associated with treating metastatic disease as well as the cost of palliative care were applied to these patients. It was assumed that 50% of patients would have received systemic chemotherapy with a regimen of cisplatin 80mg/m^2 (day 1) and fluorouracil 800mg/m^2 (day 1, 2, 3 and 4), assumed to be given for an average of four cycles. As above, systemic chemotherapy costs were by combining drug costs from eMit[20] with outpatient administration costs from NHS reference costs[18]. It was estimated that systemic chemotherapy would cost £889 per cycle (£3,555 for 4 cycles). A palliative care cost of £7,287 was applied in the model, which was based on a costing report by the Nuffield Trust[21], which estimated the average resource use of patients with cancer in the last three months of life.

The majority of the QoL values utilised in the analysis were sourced from an existing cost-utility analysis by Higgins[22]. The QoL data were differentiated depending on whether the patient was alive with a larynx that was entirely intact, partially intact (i.e. after a partial laryngectomy) or absent (i.e. after a total laryngectomy). In addition, a QoL value from the NICE HTA on cetuximab[23] was used as an estimate for patients in a metastatic disease state.

Results

The deterministic base case results of the analysis are presented in Table 4. It can be seen that in both T1a and T1b-T2 laryngeal cancer, using RT as the initial treatment strategy was more expensive (£2,654 and £623 in T1a and T1b-T2 laryngeal cancer, respectively) and less effective (reduction of 0. 141 and 0.04 in T1a and T1b-T2 laryngeal cancer, respectively) than transoral laser microsurgery (TLM). Therefore, in cost-effectiveness terms, TLM can be considered the dominant strategy i.e. more effective and less costly.

Table 4: Base case cost-effectiveness analysis for early glottis cancer

Initial treatment	**Cost**		**QALYs**		**ICER (cost per QALY)**
	Total	**Incremental**	**Total**	**Incremental**	
T1a laryngeal cancer					
Transoral laser microsurgery	£8,202		6.48		-
Radiotherapy	£10,857	£2,654	6.34	-0.14	Dominated
T1b and T2 laryngeal cancer					
Transoral laser microsurgery	£11,025		6.28		
Radiotherapy	£11,648	£623	6.23	-0.04	Dominated

A series of deterministic sensitivity analyses were conducted, whereby an input parameter was changed, the model re-run and the new cost-effectiveness result recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in the Table 5.

Table 5: One-way sensitivity analysis results for T1a and T1b-2 laryngeal cancer

Change made	**ICER (cost per QALY gained with RT)**	
	T1a	**T1b-T2**
No side effects from RT	RT Dominated	RT Dominated
No difference in local control	RT Dominated	RT Dominated
Upper local control RR = 1.03	RT Dominated	-
Lower local control RR = 0.99	RT Dominated	-
Upper DSS RR = 1.02	RT Dominated	RT Dominated
Lower DSS RR = 0.99	RT Dominated	£203,912
DSS in T1b-T2 laryngeal cancer = 85%	-	RT Dominated
DSS in T1b-T2 laryngeal cancer = 75%	-	RT Dominated
Upper recurrence and mortality RR	RT Dominated	-
Lower recurrence and mortality RR	RT Dominated	-
No difference in recurrence rates	RT Dominated	RT Dominated
No difference in QoL values	RT Dominated	RT Dominated

Change made	ICER (cost per QALY gained with RT)	
	T1a	T1b-T2
No discounting	RT Dominated	RT Dominated
Day case costs for TLM	RT Dominated	RT Dominated
TLM cost increased by 50%	RT Dominated	£8,995
TLM cost = radiotherapy cost	RT Dominated	£17,492
Same treatments in TLM and RT after first recurrence	RT Dominated	RT Dominant
Post treatment QoL with RT 0.01 higher than with TLM	RT Dominated	£26,232
Post treatment QoL with RT 0.05 higher than with TLM	£12,134	£2,093
Recurrence rates maintained over 10 years	RT Dominated	RT Dominated
16 fraction (50 Gy) radiotherapy schedule	RT Dominated	RT Dominated

It can be seen that, in the T1a laryngeal cancer group, the conclusion of the analysis is unchanged in most modelled scenarios i.e. TLM is found to be the dominant strategy in most analyses. The exception to this was when it was assumed that QoL was higher in patients treated with RT. When assuming RT was associated with QoL gains of 0.05 it became the most cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of £12,280.

In the T1b-T2 laryngeal cancer group, the analysis was found to be more sensitive with the conclusion changing in numerous scenarios. In particular, RT became the most cost-effective intervention when TLM costs were increased and in scenarios where a QoL gain was assumed for RT.

The influence of assuming a QoL benefit for patients treated with RT was further explored in a threshold analysis. The analysis showed that, at a threshold of £20,000 per QALY, RT would become cost-effective in comparison to TLM when the post treatment QoL with RT was 0.038 and 0.011 higher than that with TLM in the T1a and T1b-T2 laryngeal cancer groups, respectively.

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and a cost-effectiveness acceptability curve (CEAC) in Figures 3, 4, 5 and 6. The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The ICER scatterplot depicted in Figure 3 shows the incremental cost-effectiveness pairs for a comparison between RT and TLM in patients with T1a laryngeal cancer. The majority of the results reside in the North West showing that RT was found to be more expensive and less effective than TLM. In the CEAC presented in figure 4 for the T1a laryngeal cancer group, TLM has a 71% probability of being cost-effective at a threshold of £20,000 per QALY.

The ICER scatterplot depicted in Figure 5 shows the incremental cost-effectiveness pairs for a comparison between RT and TLM in patients with T1b-T2 laryngeal cancer. The cost-effectiveness pairs are spread across all four quadrants of the plane, suggesting that there is considerable uncertainty in this analysis. This is reflected in the CEAC presented in figure 6 for the T1b-T2 laryngeal cancer group, in which it can be seen that TLM has a 58% probability of being cost-effective at a threshold of £20,000 per QALY.

Discussion:

Synopsis of key/new findings

The results of the base case analysis suggest that using TLM as the initial treatment for early stage laryngeal cancer is a cost-effective strategy in T1a and T1b-T2 laryngeal cancer. Indeed, TLM was found to be dominant in both analyses. However, the sensitivity analysis showed that there was a difference in the level of uncertainty around the results with much more uncertainty around the results in T1b-T2 laryngeal cancer. Taking into consideration the oncologic and the health economic data, the 2016 NICE guidelines on upper aerodigestive tract cancer [1] recommends that TLM be offered as first choice intervention for patients with T1a glottis cancer.

Strengths and drawbacks of the study

This is the first study to have systematically assessed cost-effectiveness of TLM and RT for early glottis cancers, applicable to the National Health Service in the UK. As with most economic analyses, this analysis is, to some extent, dependent on the clinical data upon which it is based. A systematic review was undertaken to ensure that the model inputs reflect the best clinical evidence currently available; however, the evidence base was found to have limitations. In both T1a and T1b-T2 laryngeal cancer groups, observational studies were used as the main source of clinical data.

There was also found to be a paucity of quality of life data in this area. The key QoL values applied in this model were sourced from Higgins et al. 2011[22] which was not without limitations. Firstly, since the study was Canadian, it may not be directly applicable to the UK context. Secondly, QoL was measured using the Health Utilities Index Mark 3 rather than the NICE preferred EQ-5D. Thirdly, the small sample size (n=30) limits the certainty that can be placed in the QoL values that were obtained. While these limitations may affect the reliability go the QALY results obtained, it should be noted that

the quantity of QALY benefits was not found to be a crucial determinant of the model result. In both scenarios, TLM was found to be dominant (i.e. more effective and cheaper), thus it is the direction of the QoL values that is of most importance and these conform to expectations.

Comparisons with other studies

With the publication of several observational studies and pooled analyses, the medical community is in agreement that no evidence exists to show superiority of RT or TLM in local control or overall survival. RT may be associated with less measureable perturbation of voice as compared to surgery, but no significant differences in patient perception exist[24]. A recent systematic review of eight retrospective cohort studies describing 362 patients with a mean follow up of 47 months concluded that no significant difference in post-treatment Voice Handicap Index, a validated outcome measure, existed between these two treatments[25].

Recent studies have shown a shift towards TLM as a preferred treatment for T1a glottic cancers[26]. It is unlikely that a randomised controlled study will be performed to generate higher level evidence since previous UK-based trials regarding this (EASTER) failed to recruit adequately[27]. While it is primarily the clinical and patient factors that should be taken into consideration to plan the appropriate treatment for any given patient, cost effectiveness data can influence the treatment plan if equipoise exists.

To date, no studies have performed a cost effectiveness assessment of TLM versus RT for early glottic cancer in the UK setting. A cost-effectiveness analysis considering the Canadian health care system[22] found TLM to dominate RT with higher QALYs and lower costs. A cost analysis study from Canada showed that RT was approximately four times more expensive than TLM[28]. A study of the itemised average costs of RT and TLM in the American health care system in 2001 showed RT to be 15.5 times costlier[29]. Using the 5-year survival rate as the "effect" in a cost effectiveness analysis, Diaz-de-Cerio et al[30] found that TLM offered a saving of €1342.68 per year in the Spanish healthcare setting, concluding that TLM was the dominant option for T1 and T2 glottic cancers.

Conclusion

The results of the analysis suggest that using transoral laser microsurgery as the initial treatment for early stage laryngeal cancer is a cost-effective strategy in T1a and T1b-T2 laryngeal cancer. However, in the case of T1b-T2 laryngeal cancer, the result was found to be very sensitive to the changes made in deterministic and probabilistic sensitivity analysis. Therefore, the optimal strategy, in cost-effectiveness terms, remains uncertain in patients with T1b-T2 laryngeal cancer.

Competing interests

The authors have no competing interests to declare.

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